## SYNOPSIS

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia worldwide, affecting millions of individuals, particularly in low- and middle-income countries. The disease is characterized by progressive cognitive decline, memory impairment, and neuronal dysfunction resulting from multifactorial pathological processes. Major hallmarks of AD include amyloid-β (Aβ) plaque formation, neurofibrillary tangles composed of hyperphosphorylated tau protein, cholinergic neuronal degeneration, oxidative stress, mitochondrial dysfunction, inflammation, and disruption in neurotransmitter and metal ion homeostasis. Although several FDA-approved drugs such as donepezil, memantine, rivastigmine, galantamine, aducanumab, and lecanemab provide symptomatic relief, they do not effectively halt disease progression. Therefore, the development of multi-target-directed ligands (MTDLs) capable of modulating multiple pathological pathways has emerged as a promising therapeutic strategy.

The present research focuses on the design, synthesis, and biological evaluation of chromenone-based derivatives as potential multi-target agents against AD-related enzymes, particularly β-secretase (BACE1), acetylcholinesterase (AChE), and butyrylcholinesterase (BuChE), along with antioxidant activity. Initially, bioactive chromenone phytochemicals were screened through molecular docking and in silico ADMET studies, leading to the selection of 8-methoxypsoralen (8-MOP) for semi-synthetic modification. Semi-synthetic derivatives demonstrated significant binding interactions with key catalytic residues of BACE1 and showed favourable drug-likeness, gastrointestinal absorption, and blood–brain barrier permeability. Several compounds exhibited potent in vitro inhibition against BACE1, AChE, and BuChE, along with strong antioxidant potential, indicating their capability as multi-target therapeutic candidates.

Furthermore, two series of synthetic chromenone derivatives, namely heterocyclic amino-acetyl chromenones and heterocyclic carboxamide chromenones, were designed and synthesized using multi-step synthetic approaches. Molecular docking studies confirmed strong interactions with crucial BACE1 residues, while in silico ADMET analysis demonstrated acceptable pharmacokinetic properties. Biological evaluation revealed promising inhibitory activity against AD-related enzymes and effective free radical scavenging properties. Certain compounds, particularly 3h, 5c, and 4c, displayed excellent multi-target activity, favourable physicochemical characteristics, and encouraging safety profiles, highlighting their potential as lead molecules for AD drug development.

Overall, this study establishes chromenone derivatives as promising scaffolds for the development of next-generation anti-Alzheimer's agents. The findings emphasize the importance of structural modifications influencing polarity and hydrophobicity in achieving effective multi-target inhibition. Future research should focus on expanded biological validation, pharmacokinetic evaluation, and optimization to advance these compounds toward clinical applications.